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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,461	04/17/2001	Robert Leroy Heinrikson	6309.N CP	8815

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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,461	HEINRIKSON ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 34-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5, 7* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Claims 1-46 are still at issue and are present for examination. Claims 21-33 are now under consideration. Claims 1-20, 32-46 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group II, Claims 21-33 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that coexamination of all of Groups I, II and III through VI would not constitute undue burden on the Examiner and that searching polypeptides would automatically provide corresponding nucleic acid sequences. This is not found persuasive because not all databases provide links to both polypeptide and polynucleotides. Furthermore, the search does not involve only public databases and involves searching patent databases as well. In addition to the above polynucleotides and polypeptides are considered as distinct and separate inventions with separate classification and requiring separate searches. Therefore contrary to applicant's argument while the search for the groups may overlap to some extent, they are not coextensive. Also, the search for Groups I and III through VI would each require the search of subclasses unnecessary for the search of elected Group II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-20, 32-46 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicants fail to recite corresponding SEQ ID NO for sequences depicted in figures or figure description. See particularly 37 CFR 1.821(d).

Specification

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 29-45 have been renumbered 30-46.

Claim Objections

Claim 33 is objected to because of the ~~following informalities:~~ Claim 33 depends from non-elected claim 43. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 21 and 22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 21 and 22 are directed to a human heparanase which reads on a product of nature. Amending the claim to recite "an isolated human heparanase.." to show the hand of man would overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 21 and 22 are dependent from a non-elected invention rendering them indefinite in the context of claim examination.

Claims 23-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 23-33 are drawn to an enzyme labeled as ~~"heparanase II"~~. It is not clear to the Examiner as to how one skilled in the art will be able to distinguish "heparanase II" from other human heparanase already disclosed in the prior art. A perusal of the specification does not provide a specific or a distinguishing assay based on which the instant enzyme can be

identified as "heparanase II". The only information that is provided is that the instant enzyme has an amino acid sequence that is different from that already disclosed in the prior art (figure 2). Therefore, it is not clear to the Examiner as to whether the instant is a simple variant of the already known heparanase or an entirely different class of heparanase and as to how those skilled in the art can identify the above protein without first analyzing its amino acid sequence.

Claims 23, 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 23, 26-29 are directed distinctly to human heparanase polypeptides comprising amino acids 42 through 129 and amino acids 130 through 534 and amino acids 42 through 161 and 162 through 534. It is not clear to the Examiner as how two fragments cleaved from a single enzyme with a single catalytic region continues to be active even after their separation. It is not clear whether the above enzyme has two catalytic sites both of which equally active when residing in a single polypeptide. A perusal of the specification does not provide any such characteristics of the enzyme except for the identification of the signal peptide sequence.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 22, 23 (parts c-f), 26, 27, 28, 29, and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme of with SEQ ID NO:2,

having heparanase activity or an enzyme comprising amino acids 42 through 534 or amino acids 130 through 534 and having heparanase activity, does not reasonably provide enablement for any or all such enzymes from the human source or such enzymes comprising amino acids 42 through 129 or 42 through 161 or 130 through 534 or 162 through 534 of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 21, 22, 23 (parts c-f), 26, 27, 28, 29, and 33 are so broad as to encompass any or all human heparanases including variants, mutants and recombinants, human heparanase comprising amino acids 42 through 129 or 42 through 161 or 130 through 534 or 162 through 534 of SEQ ID NO:2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the fragments broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins'

structure relates to its function. Furthermore, since the catalytic sequence is essential for the enzyme activity, fragments of enzymes not encompassing catalytic sequences may not continue to have the same catalytic activity. Similarly, since enzymes are generally known to have a single catalytic sequence or site, cleavage of the enzyme into two fragments and claiming that both the fragments continues to have the same enzymatic activity requires a knowledge of and guidance with regard to such activity in the fragments. Applicants have failed to provide such a teaching or guidance. Therefore, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence SEQ ID NO:2 or amino acids 42-534 having heparanase activity. It would require undue experimentation by the skilled artisan to make and use the claimed polypeptides with an undefined function/activity. The specification is limited to teaching the making and use of SEQ ID NO: 2 or amino acids 42-534 of SEQ ID NO:2 as a heparanase but provides no guidance with regard to the making of variants fragments or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for a large number of variants, mutants or fragments, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be

made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all or any human heparanase and modifications of SEQ ID NOS:2 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting heparanase activity; (B) the general tolerance of heparanase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying amino acid residues in SEQ ID NO:2 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including fragments of SEQ ID NO:2 without showing that such fragments have activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of fragments of SEQ ID NO:2 having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 21, 22, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 21, 22, are directed to human heparanase polypeptides (all or any human heparanases). Claims 21, 22, are rejected under this section of 35 USC 112 because the claims are directed to a genus of human heparanase polypeptides that have not been disclosed in the specification. No description has been provided of all the polypeptide sequences encompassed by the claim. No information, beyond the characterization of the function has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences encompassed by the claims, including fragments within the scope of the claimed genus. The genus of polypeptides claimed is a variable genus including peptides which have different structures. Therefore structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 23 (parts c-f), 26, 27, 28, 29, and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 23 (parts c-f), 26, 27, 28, 29, and 33 are directed to polypeptide fragments corresponding to portions of the sequence of SEQ ID NO:2. Claims 23 (parts c-f), 26, 27, 28, 29, and 33 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:2 that have not been described in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the function of all the polypeptide sequences derived from SEQ ID NO:2, including fragments within the scope of the claimed genus. The genus of polypeptides claimed is a variable genus including peptides which may or may not have the said function. Therefore functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Freeman et al. (Biochem J., 1998, Vol. 330:1341-1350). This rejection is based upon the public availability of a printed publication. Claims 21-22 of the instant application are drawn to a human heparanase and a composition comprising the same. Freeman et al. disclose a human heparanase and a composition comprising the same. Therefore, Freeman et al. anticipate claims 21-22 of this application as written.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21-23, 26-27 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Fiscella et al. (Accession No. AAU07424, 12-18-01 and WO 01/79253, Oct, 2001, filed on 4-11-01 with an effective US filing date 4-18-00, published in English with US as a designated State, Jumbo Document, 308 pages). This rejection is based upon the public availability of a printed publication. Claims 21-23, 26-27 and 33 of the instant application are drawn to a human heparanase, a composition comprising the same, human heparanase comprising amino acids 42-129 or 42-161 of SEQ ID NO:2. Fiscella et al. disclose a human heparanase, a composition comprising the same, human heparanase comprising amino acids 42-129 or 42-161 of SEQ ID NO:2 (see enclosed sequence alignment). Thus Fiscella et al. anticipate claims 21-23, 26-27 and 33 of this application as written.

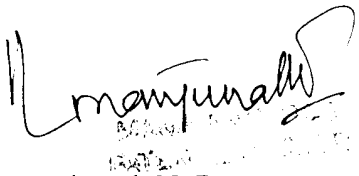
Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
May 18, 2003